REMARKS / ARGUMENTS

Claims Currently Pending

Claims 1-12 are pending.

Claim Rejections – 35 USC 112

Lack of Enablement Basis for Rejection ("hydrates")

The rejection of claims 1-11 under 35 USC 112, first paragraph, for lacking enabling support for hydrates has been maintained. This basis for rejection of claims 1-11 is traversed for the following reasons.

The term "hydrates" essentially has two, very different meanings.

It is apparent that in making the rejection the Office is assuming that the term hydrate means a product which results from the chemical reaction of water with a host molecule. When used in this way the hydrate is different from the host molecule. The following references define the term hydrate in this sense.

> The Concise Oxford Dictionary, Ninth Edition
> • *n.* a compound of water combined with another compound or with an element. • *v.tr.* **1a** combine chemically with water. b (as hydrated adj.) chemically bonded to water. **2** case to absorb water.
>
> Merriam-Webster's Collegiate Dictionary, Electronic Edition, Version 1.5
> a compound formed by the union of water with some other substance.
>
> The Random House Dictionary of the English Language, The Unabridged Edition, © 1969.
> -*n.* 1. any of a class of compounds containing chemically combined water. In some hydrates, as washing soda, $Na_2CO_3 \cdot 10H_2O$, the water is loosely held and is easily lost on heating; in others, such as sulfuric acid, $SO_3 \cdot H_2O$, or H_2SO_4, it is strongly held as water of constitution. –*v.t., v.i.* 2. to combine chemically with water.
>
> Wikipedia
> In organic chemistry, a hydrate is a compound formed by the addition of water to a host molecule. Thus ethanol could be considered to be the hydrate of ethylene. These substances do not contain water as such, but have their constituents (hydrogen, oxygen, hydroxyl) so arranged that water may be eliminated. Hence, hydrates are derivatives of, or compounds with, hydroxyl. One such example is chloral hydrate.

On the other hand, those of skill in the art will readily understand, from context, that the term hydrate, as used in the present application, is intended to mean a solid compound containing water molecules combined in a definite ratio as an integral part of the crystal. When used in this way the term does not connote a reaction product of the compound with water. That is to say, the hydrate is not chemically different than the molecule per se. The following references define the term hydrate in this latter sense.

> The American Heritage® Dictionary of the English Language, Fourth Edition copyright ©2000 by Houghton Mifflin Company. Updated in 2003. Published by Houghton Mifflin Company
> -*n.* A solid compound containing water molecules combined in a definite ratio as an integral part of the crystal.
>
> United States Food and Drug Administration Guidance for Industry: ANDAs: Pharmaceutical Solid Polymorphism
> Solvates are crystal forms containing either stoichiometric or nonstoichiometric amounts of a solvent. **If the incorporated solvent is water, the solvate is commonly known as a hydrate.** (Emphasis added)

Accordingly, the term hydrate, as used in the application, does not mean a separate chemical entity or a different compound. Rather the term hydrate refers to a solid, crystalline form of a compound per se, wherein water molecules are combined in a definite ratio as an integral part of the crystal lattice. Persons of ordinary skill in the art fully understand that many compounds can exist in either anhydrous or hydrated crystalline forms, and they understand, in general, how to convert an anhydrous crystalline form to a hydrated crystalline form. Indeed, many anhydrous substances spontaneously convert to hydrates upon exposures to moisture. In view of the background knowledge possessed by those of ordinary skill in the art, the specification is clearly enabling for the production of hydrates, meaning crystalline forms of the claimed compounds per se that contain water in their crystal lattice.

Written Description Basis for Rejection

Claims 11 and 12 also stand rejected under 35 USC 112, first paragraph, as failing to comply with the written description requirement, for the reasons discussed below.

Claim 12 is directed to a "method for treating or reducing the frequency of headache, migraine headache or cluster headache". The action states, incorrectly, that there is no antecedent basis for this in the specification. More specifically, the action is incorrect when

it asserts that the specification does not describe the treatment of any "physio-pathology", as is claimed in claim 12. On the contrary, the specification states, at page 105, lines 21-23, "In view of their pharmacological properties the compounds of general formula I and the salts thereof with physiologically acceptable acids are thus suitable for the acute and prophylactic treatment of headaches, particularly migraine or cluster headaches." The action is also not correct in asserting that the specification does not show that the claimed compounds have biological activity, such as binding activity, that would support the assertion that they are suitable for the acute and prophylactic treatment of headaches, particularly migraine or cluster headaches. Two in vitro experiments are described in the specification, at pages 104-105. The results obtained from the first experiment, entitled "Binding studies with SK-N-MC cells (expressing the human CGRP receptor)" show that the claimed compounds exhibit IC_{50} values $\leq$ 10000 nM in the test described. The results of the second experiment, entitled "CGRP Antagonism in SK-N-MC cells", show that the claimed compounds exhibit CGRP-antagonistic properties in the in vitro test model described, in a dosage range between 10-12 and 10-5 M. Moreover, at page 106, lines 7-11, the specification provides a dosage range within which the compounds may be employed in order to carry out the claimed method.

It is accordingly quite clear that claim 12 is directed to subject matter that is described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

New Matter Basis for Rejection

The action further rejects claim 12, stating that the phrase "host having an increased risk of suffering from a headache, migraine headache or cluster headache" is considered to be new matter. It is respectfully asserted that this additional reason for the rejection lacks proper foundation and should be withdrawn, for the reasons given below.

Claim 12 is a process claim. As with any process claim, claim 12 entails the performance of an action X, upon some recipient of the action Y, for some useful purpose Z. In the case of claim 12 the action X to be performed is a medical treatment, more specifically "the administration *** of an effective amount of a compound according to claim 1 or a

physiologically acceptable salt thereof". The recipient Y of the action X is "a host currently suffering from a headache, migraine headache or cluster headache, or a host having an increased risk of suffering from a headache, migraine headache or cluster headache" and the useful purpose Z is "treating or reducing the frequency of headache, migraine headache or cluster headache".

At this point it should be observed that claim 12 could have been written as follows, leaving out any explicit description or identification of the recipient of the action:

> Claim 12 (as it ~~might~~ have been written): A method for treating or reducing the frequency of headache, migraine headache or cluster headache which comprises the administration~~, to a host currently suffering from a headache, migraine headache or cluster headache, or a host having an increased risk of suffering from a headache, migraine headache or cluster headache,~~ of an effective amount of a compound according to claim 1 or a physiologically acceptable salt thereof.

Drafting claim 12 in the above manner would surely have avoided the stated new matter rejection, but it would arguably have rendered the claim indefinite by not explicitly identifying the recipient of the action (the medical treatment). To avoid any possibility of indefiniteness, claim 12 expressly states that the recipient of the medical treatment is (when treating headache, migraine headache or cluster headache) "a host currently suffering from a headache, migraine headache or cluster headache" or (when reducing the frequency of headache, migraine headache or cluster headache) "a host having an increased risk of suffering from a headache, migraine headache or cluster headache". Claim 12 was written as it is to avoid such possibility of indefiniteness.

Does the specification provide antecedent basis for the useful purpose or process of claim 12, which is "treating or reducing the frequency of headache, migraine headache or cluster headache"? Yes it does. As mentioned before, the specification states, at page 105, lines 21-23, "In view of their pharmacological properties the compounds of general formula I and the salts thereof with physiologically acceptable acids are thus suitable for the acute and

prophylactic treatment of headaches, particularly migraine or cluster headaches." The terms "acute" and "prophylatic" treatment have art-recognized meanings, when used in the present context. It is well established in the field of medicine that migraine headaches may be treated during an attack (acute or abortive treatment), or they may be treated preventively or prophylactically (to reduce the number or frequency of attacks in patients who experience frequent migraines). As support for these statements, see the web page "Migraine, MayoClinic.com", the web page "Migraine, the National Migraine Association: Current Treatment Methods", and J Headache Pain (2001) 2:147–161, copies of which are provided. Thus, in stating that the compounds "are *** suitable for the acute and prophylactic treatment of headaches, particularly migraine or cluster headaches", the specification describes a useful purpose for the claimed process or method that would be readily understood by those of skill in the relevant art. This description of the useful purpose of the method corresponds essentially to that in claim 12.

Does the specification provide antecedent basis for the action to be performed in carrying out the method of claim 12, which is "administration of an effective amount of a compound according to claim 1 or a physiologically acceptable salt thereof"? Yes it does. At page 106, lines 7-11, the reader is instructed to administer the compounds via various routes, within specified dose ranges. This informs the reader what amount of a compound would need to be administered in order to be effective for carrying out the claimed method.

Finally, does the specification provide antecedent basis for the identification of the recipient of the action to be performed in carrying out the claimed method? Not explicitly, but this is trivial and of no consequence. Again mentioning the references listed above, it is clear that one of skill in the medical art would appreciate that when one treats a headache, migraine headache or cluster headache the recipient of that treatment must logically be "a host currently suffering from a headache, migraine headache or cluster headache". Similarly, when one reduces the frequency of headache, migraine headache or cluster headache the recipient must logically be "a host having an increased risk of suffering from a headache, migraine headache or cluster headache".

It follows that claim12, by including the phrase "host having an increased risk of suffering from a headache, migraine headache or cluster headache", is merely explicitly stating what is already implicit and in fact inherent in the explicitly stated useful purpose of the treatment. The nature of the subject or host to be treated is so readily apparent from the stated purpose of the treatment that it is not necessary for the specification to state it explicitly. Accordingly, the noted phrase is not new matter.

Rejection of Claim 11

It is respectfully asserted that the action does not adequately explain the basis for rejection of claim 11. Elaboration and clarification is requested should this rejection be maintained.

Claim Rejections – 35 USC 103(a)

Rejections as Unpatentable Over Rudolf et al., Supplemented with CA 128:257695

It is urged that the rejection of claims 1-12 under 35 USC 103(a) as unpatentable over Rudolf et al., US 6,344,449, supplemented with CA 128:257695 is overcome by the claim amendments made herein, for the reasons given below.

In claim 1, as now amended, the definitions of X, U, V and W have been reduced in scope. Basis for so amending the definitions of these groups can be found on page 19 of the specification, under point (iii), where it is said, "....while in all the embodiments mentioned above those compounds wherein ..... (iii) A denotes an oxygen atom, X denotes an oxygen atom, an imino or methylene group, U denotes a trifluoromethyl or pentafluoroethyl group, V denotes an amino or hydroxy group and W denotes a hydrogen, chlorine or bromine atom or a trifluoromethyl group, are of most particularly outstanding importance."

Dependent claims 2-8 and 10-12 are similarly restricted in scope, as they incorporate by reference the definitions of X, U, V and W found in claim 1.

Claim 9 has been amended by the deletion of all species no longer embraced by the genus described by claim 1.

The amended claims are now directed, more narrowly, to the core of the invention, which is characterized by the substitution pattern of the phenyl ring wherein V denotes an amino or hydroxy group.

The amended claims are directed to compounds that differ essentially from the one cited by the Examiner as nearest state of the art (US '449, compound 606). It would not have been obvious for a person skilled in the art that the compounds now claimed, which are structurally quite different than those of the cited prior art, would have similar activities as those of the prior art. In the compounds of the amended claims, the allocation of the electric charge at the phenyl ring is different than that of compound (606) of US '449.

Applicant retains the right to pursue claims to the deleted subject matter in a continuation application.

Rejections as Unpatentable Over Mallee et al. in view of Rudolf et al.

It is urged that the rejection of claims 1-12 under 35 USC 103(a) as unpatentable over Mallee et al. CA 137:304712 in view of Rudolf et al. US 6,344,449 is overcome by the claim amendments made herein, for the reasons given above.

Claim Rejections – Nonstatutory Obviousness-type Double Patenting

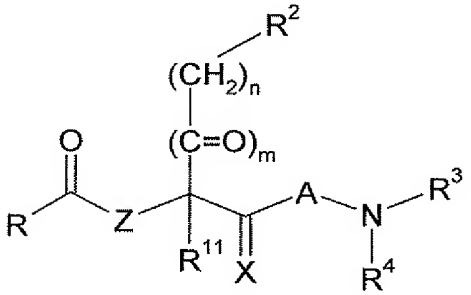
Rejection of Claims 1-12 as Unpatentable Over Rudolf et al., Supplemented with CA 128:257695

It is urged that the rejection of claims 1-12 on the ground of nonstatutory obviousness-type double patenting, as unpatentable over Rudolf et al., US 6,344,449, supplemented with CA 128:257695 is overcome by the claim amendments made herein. As explained above, the claims as amended are directed to compounds that are structurally significantly different than the two compounds claimed by US 6,344,449. In view of these differences it is urged that there is no prima facie structural obviousness and that, accordingly, there is no nonstatutory obviousness-type double patenting.

Provisional Rejection of Claims 1-12 as Unpatentable Over Co-Pending 10/835,495 in view of CA 128:257695

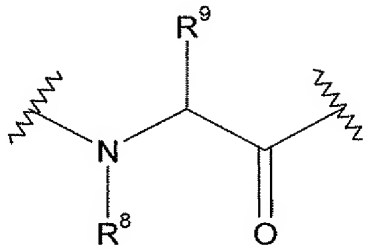
It is urged that the provisional rejection of claims 1-12 on the ground of nonstatutory obviousness-type double patenting, as unpatentable over co-pending 10/835,495 in view of CA 128:257695 is improper and should be withdrawn in that the pending claims are not prima facie obvious over claims 15-19 of co-pending 10/835,495.

The claims of the co-pending application are directed to compounds of the formula I



(I),

wherein the moiety A is a divalent group of formula



(III),

that is linked to the group $-NR^3R^4$ of formula (I) via the carbonyl group.

The compounds of the claims in the present application lack a structural feature that corresponds to the moiety A of the co-pending application. The Examiner has not explained why the compounds of the present claims are prima facie obvious variants of those covered by the claims of the co-pending application, even though they lack this structural feature.

Provisional Rejection of Claims 1-12 as Unpatentable Over Co-Pending 10/683,921 in view of US 6,344,449

Claims 1-12 of the present application are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-14 of co-pending 10/683,921 in view of US 6,344,449. This provisional rejection is traversed because SN 10/683,921 does not appear to be a valid application serial number. Clarification is requested.

In the event that the Examiner intended to base the rejection upon SN 10/685,921 it should be noted that Applicant would stand ready to overcome such rejection, when it becomes non-provisional, with a terminal disclaimer.

Provisional Rejection of Claims 1-12 as Unpatentable Over Co-Pending 10/755,593, 11/107,052 and 11/107,195, each in view of US 6,344,449

Claims 1-12 of the present application are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-14 of co-pending 10/775,593 in view of US 6,344,449. This provisional rejection is traversed for the following reason.

It is respectfully asserted that, in view of the foregoing amendments and arguments, no grounds for rejection remain in the present application, aside from the present obviousness-type double patenting rejections.

Reference is made to the discussion of double patenting rejections in MPEP Section 804, and in particular to the discussion respecting provisional obviousness-type double patenting (ODP) rejections between copending applications having a common owner or assignee.

In this regard, it should be noted that the present application and the three copending applications cited are co-owned.

MPEP Section 804 states as follows:

> If a "provisional" nonstatutory obviousness-type double patenting (ODP) rejection is the only rejection remaining in the earlier filed of the two pending applications, while the later-filed application is rejectable on other grounds, the examiner should withdraw that rejection and permit the earlier-filed application to issue as a patent without a terminal disclaimer.

As shown by the table below, the present application is earlier filed than copending 10/755,593, 11/107,052 and 11/107,195. Accordingly, and in view of the instruction given by MPEP 804, the Office should withdraw the ODP rejection to the extent that it is based upon these three co-pending applications.

Application	U.S. Filing or 371(c) Date
10/687,262 (present application)	10/16/2003
10/755,593 (copending)	1/12/2004
11/107052 (copending)	4/15/2005
11/107195 (copending)	4/15/2005

Respectfully submitted,

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Co-transmittals

(1) PDF copy of web page "Migraine, MayoClinic.com"
(2) PDF copy of web page "Migraine, the National Migraine Association: Current Treatment Methods"
(3) PDF copy of J Headache Pain (2001) 2:147–161

HEADACHE

Aug 15, 2007

Migraine

ARTICLE SECTIONS

Treatment

A variety of drugs have been specifically designed to treat migraines. In addition, some drugs commonly used to treat other conditions also may help relieve or prevent migraines. Medications used to combat migraines fall into two broad categories:

- **Pain-relieving medications.** Also known as acute or abortive treatment, these types of drugs are taken during migraine attacks and are designed to stop symptoms that have already begun.
- **Preventive medications.** These types of drugs are taken regularly, often on a daily basis, to reduce the severity or frequency of migraines.

Choosing a strategy to manage your migraines depends on the frequency and severity of your headaches, the degree of disability your headaches cause, and your other medical conditions. You may be a candidate for preventive therapy if you have two or more debilitating attacks a month, if you use pain-relieving medications more than twice a week, if pain-relieving medications aren't helping, or if your migraine signs and symptoms include a prolonged aura or numbness and impaired movement on one side of your body.

Some medications aren't recommended if you're pregnant or breast-feeding. Some aren't used for children. Your doctor can help find the right medication for you.

Pain-relieving medications

For best results, take pain-relieving drugs as soon as you experience signs or symptoms of a migraine. It may help if you rest or sleep in a dark room after taking them:

- **Nonsteroidal anti-inflammatory drugs (NSAIDs).** These medications, such as ibuprofen (Advil, Motrin, others) or aspirin, may help relieve mild migraines. Drugs marketed specifically for migraine, such as the combination of acetaminophen, aspirin and caffeine (Excedrin Migraine), also may ease moderate migraines, but aren't effective alone for severe migraines. If over-the-counter medications don't help, your doctor may suggest a stronger, prescription-only version of the same drug. If taken too often or for long periods of time, NSAIDs can lead to ulcers, gastrointestinal bleeding and rebound

headaches.

- **Triptans.** For many people with severe migraine attacks, triptans are the drug of choice. They are effective in relieving the pain, nausea and sensitivity to light and sound that are associated with migraines. Sumatriptan (Imitrex) was the first drug specifically developed to treat migraines. Related medications include rizatriptan (Maxalt), naratriptan (Amerge), zolmitriptan (Zomig), almotriptan (Axert), frovatriptan (Frova) and eletriptan (Relpax). Side effects of triptans include nausea, dizziness, muscle weakness and, rarely, stroke and heart attack. In recent studies, a single-tablet combination of sumatriptan and naproxen sodium relieved migraine symptoms more effectively than did either individual medication. This combination tablet will likely be marketed soon.

- **Ergots.** Ergotamine (Ergomar) has been in use for more than 60 years and was a common prescription for migraine before triptans were introduced. Ergotamine is much less expensive, but also less effective, than triptans. Dihydroergotamine is an ergot derivative that is more effective and has fewer side effects than ergotamine.

- **Anti-nausea medications.** Since migraine attacks are often accompanied by nausea with or without vomiting, medication for treatment of these symptoms is appropriate and is usually combined with other medications. Frequently prescribed medications are metoclopramide (oral) or prochlorperazine (oral or rectal suppository).

- **Butalbital combinations.** Medications that combine the sedative butalbital with aspirin or acetaminophen are sometimes used to treat migraine attacks. Some combinations also include caffeine or codeine. These medications, however, have a high risk of rebound headaches and withdrawal symptoms and accordingly should be used infrequently.

- **Opiates.** Medications containing narcotics, particularly codeine, are sometimes used to treat migraine pain when people can't take triptans or ergots. These drugs are habit-forming and are usually used only as a last resort.

Preventive medications

Preventive medications can reduce the frequency, severity and length of migraines and may increase the effectiveness of symptom-relieving medicines used during migraine attacks. Your doctor may recommend that you take preventive medications daily, or only when a predictable trigger, such as menstruation, is approaching.

In most cases, preventive medications don't eliminate headaches completely, and some can have serious side effects. For best results, take these medications as your doctor recommends:

- **Cardiovascular drugs.** Beta blockers — which are commonly used to treat high blood pressure and coronary artery disease — can reduce the frequency and severity of migraines. These drugs are considered among first-line treatment agents. Calcium channel blockers, another class of cardiovascular drugs, especially verapamil (Calan, Isoptin), also may be helpful. In addition, the antihypertensive medications lisinopril (Prinivil, Zestril) and candesartan (Atacand) are useful migraine prevention medications. Researchers don't understand exactly why all of these cardiovascular drugs prevent migraines. Side effects can include dizziness, drowsiness or lightheadedness.

- **Antidepressants.** Certain antidepressants are good at helping prevent all types of headaches, including migraines. Most effective are tricyclic antidepressants, such as amitriptyline, nortriptyline (Pamelor) and protriptyline (Vivactil). These medications are considered among first-line treatment agents and may reduce migraines by affecting the level of serotonin and other brain chemicals. You don't have to have depression to benefit from these

drugs. Newer antidepressants, however, generally aren't as effective for migraine prevention.

- **Anti-seizure drugs.** Although the reason is unclear, some anti-seizure drugs, such as divalproex sodium (Depakote) and topiramate (Topamax), which are used to treat epilepsy and bipolar disease, seem to prevent migraines. Gabapentin (Neurontin), another anti-seizure medication, is considered a second-line treatment agent. In high doses, however, these anti-seizure drugs may cause side effects, such as nausea and vomiting, diarrhea, cramps, hair loss and dizziness.
- **Cyproheptadine.** This antihistamine specifically affects serotonin activity. Doctors sometimes give it to children as a preventive measure.
- **Botulinum toxin type A (Botox).** Some people receiving Botox injections for their facial wrinkles have noted improvement of their headaches. The mechanism by which Botox might prevent migraines is unclear, although the drug may cause changes in your nervous system that modify your tendency to develop migraines. Studies using Botox injections for migraines have had mixed results. Additional research is necessary. Still, if several other preventive medications have failed to control your headaches, you might talk to your doctor about trying Botox.

PREVIOUS | | NEXT: Prevention

RELATED

- Migraine with aura
- Migraine headache guide

MayoClinic.com Bookstore

- 'Mayo Clinic EmbodyHealth Guide to Self-Care' (Softcover)
- 'Mayo Clinic on Headache' (Softcover)

ARTICLE TOOLS
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By Mayo Clinic Staff
Jun 6, 2007

DS00120

MIGRAINE AWARENESS GROUP: A NATIONAL UNDERSTANDING FOR MIGRAINEURS

M.A.G.N.U.M.

THE NATIONAL MIGRAINE ASSOCIATION

ABOUT MAGNUM
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WHERE TO TURN FOR HELP
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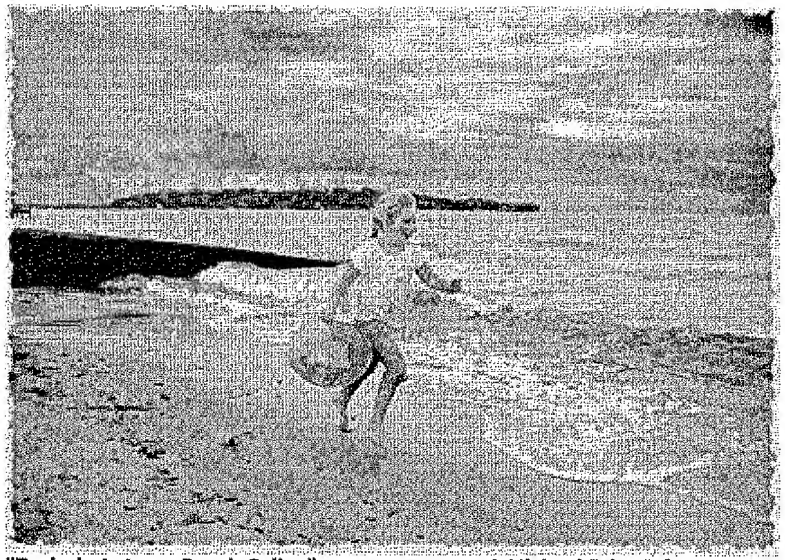
Current Treatment Methods



"Taylor's Autumn Beach Gallop"

A looming storm front can disrupt the free spirit of a day at the beach for a Migraineur. Better understanding of triggers such as barometric pressure changes induced by changing weather can help a suffer, or their parent, take appropriate preemptive abortive or other medication. Stopping a severe Migraine before it becomes severe, offers the best way to enjoy planned events, such as a fun of a playful autumn afternoon at the beach.

Many breakthroughs regarding the biological and genetic causes of Migraine have been made in recent years. And while certain of the exact biological mechanisms are still being studied, breakthroughs in treatment offer hope and relief for millions of people who suffer from the pain of Migraine.

MAGNUM has noted that in the past, Migraine tended to be managed in a way that either prescribed drugs that helped **prevent** attacks OR prescribed drugs that treated pain **during** an attack, but not both. However, the best approach to Migraine management is what MAGNUM calls a **MULTIFACTORAL approach, *which involves addressing all four aspects of Migraine health care: preventive treatment, trigger management, abortive treatment, and general pain management.***

MAGNUM's Multifactoral Approach	
I	Preventative or Prophylactic
II	Trigger Management
III	Attack Aborting
IV	General Pain Management

(I) *Preventive or Prophylactic*

***First,* preventive, or prophylactic**, medications are prescribed to prevent or reduce the number of attacks in patients who experience frequent Migraines, typically two or more per month. In general, these medications act over time to prevent blood-vessel swelling; however, they do not treat the Migraine-associated symptoms and are non-selective. Many sufferers using preventive treatments will still have to take attack-aborting medications to relieve pain and other symptoms.

Beta-blockers are the most commonly prescribed prophylactic treatment for Migraine and are considered to be an effective preventive treatment. Medication includes propranolol. Click here for more detailed information.

Antidepressants are believed to have a possible effect on serotonin or possible analgesic effects. Click here for more detailed information.

Calcium channel blockers are also used to decrease the frequency of Migraine attacks. It is thought that calcium channel blockers play a role in vessel constriction. Click here for more detailed information.

Methysergide is thought to block the inflammatory and vessel-constricting effects of serotonin. Because of potential side-effects, methysergide is generally used only on select patients. This medication also requires a four to six week drug hiatus every six months. Click here for more detailed information.

Divalproex Sodium (Depakote®) is probably the most promising of the preventive regiments currently available for Migraine. This drug was originally developed for Epilepsy; a disease often referred to as a sister disorder to Migraine, prescribed in much smaller doses when used to treat Migraine thus lessening the mild side effects.

Non-drug Alternatives to Preventative Treatment of Migraines

Gut Brain Therapy ™ MAGNUM looks into the exciting work that ForeverWell is doing in Migraine research & the gut brain. An intriguing possibility is beginning to develop. The growing evidence supporting our long term belief that Migraine is a brain disorder coupled with the work showing a second brain in the gut might cause some to look at proper neuropeptide/neurotransmitter production by the digestive system as a root cause of the factors leading to Migraine.

One company doing just that has recently published an outcome based study in which they focus primarily on healing and improving digestive dysfunction that they believe on some level is occurring in most Migraine sufferers. Synergistically, they provide nutritional support to the liver and kidney believing that these organs are critical in balancing internal function.

This natural Migraine prevention approach has shown very positive results in their initial study. Interestingly, some of the comments from study participants included that while on the nutritional supplements they found that the Migraines they did get were less severe and a lower dose of various pain treatments seemed to be more effective.

80% of the 40 study participants reported good to dramatic benefit from this approach. 20% had no benefit. In 60% of the cases the participants quality of life rating was in the 80 to 100 range indicating a virtually Migraine free condition. To learn more about Gut Brain Therapy™ and to read the entire study visit, www.foreverwell.com.

Michael Gershon, MD of Columbia University is the recognized father of the growing field of neurogastroenterology and author of *The Second Brain*. His book is fascinating and may explain why ForeverWell is getting great results with Migraine by focusing on the digestive system. For a FREE, chapter by chapter, description of the book you can send an email request to gutbrain@verizon.net.

There is a book called *The Second Brain* by Michael Gershon, MD. He is at Columbia University in New York and seems to be the leading authority in neurogastroenterology. The book is quite fascinating and perhaps does explain why ForeverWell has been getting great results with Migraine by treating the gut.

For more information:

- Take a look at Michael Gershon, MD's book *The Second Brain* and how it supports and points to the possibilities that healing the gut could help the brain.
- Review Gary Zaloga, MD's book *Nutrition in Critical Care* and how small chain peptides may provide an explanation of ForeverWell's preliminary success.
- Visit the ForeverWell website, www.foreverwell.com and read the details and explanation of their work and approach to treating Migraine.

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Petasites Hybridus (Butterbur root) is a new non-drug preventive treatment available in the United States. It is available under the name of Petadolex™ from the well respected German firm of Weber & Weber. In recent double blind studies it was shown 77% effective as a Migraine prophylaxis. Dose is one 50mg capsule twice a day.

Feverfew Leaf is a good non-drug preventitive treatment you may want to explore. Its main uses are for migraines and arthritis. Studies at the London Migraine Clinic have increased interest in this herb. This herb continues to undergo extensive scientific investigation of the parthenolide content, and how it normalizes the funtion of platelets in the blood system by inhibiting platelet aggregation, reducing serotonin release from platelets and blocking the formation of pro-inflamatory mediators. Seventy percent of the patients in these studies report fewer attacks of migraines and less painful attacks. Researchers believe that Feverfew prevents the spasms of blood vessels in the head that trigger migraines. This herb also relieves the inflammation associated with arthritis. Other benefits include: relief from nausea and vomiting; improvement of digestion; more restful sleep; and, relief of dizziness, brain, and nerve pressure.

Vitamin B2 supplements is another preventative non-drug treatment you may want to consider taking. A

study in Belgium found that people who took 400 milligrams of vitamin B2 daily had about one-third fewer migraines than did those taking a placebo. The study, published in the February issue of the journal Neurology, included 55 patients in Belgium and Luxembourg who normally had two to eight migraine attacks each month.

Magnesium as an alternative preventive treatment has mixed support in the medical community. The most current position on this alternative over the counter preventive approach is best summarized by the Migraine and headache expert Ninan T. Mathew, M.D., which he noted the following at the 1998 AASH (American Association for the Study of Headache) Scottsdale Symposium-"Even though magnesium deficiency in the brain is implicated in the pathophysiology of Migraine, there is still no proof that magnesium replacement is of any benefit in Migraine prophylaxis. The only double-blind placebo controlled study in patients with Migraine without aura (69 patients) reported negative results, even though a previous small study in menstrual Migraine reported magnesium to be effective. Mauskop et al emphasized the importance of serum ionized magnesium measurements in determining the magnesium state in Migraine patients and have used intravenous magnesium in patients found to have low ionized magnesium level. These observations have not been confirmed yet."

Perhaps oral magnesium supplementation should be a part of treatment for migraine as a preventive. Taking a 100% of the USDA recommended DV (daily value) would be safe and prudent. That would be 400mg of magnesium (from magnesium oxide or magnesium sulphate) a day.

A Canadian approach suggested that physicians advise migraine patients to consume at least 6 mg magnesium per day for each kilogram of body weight. An even higher intake of 10 mg/day per Kg of body weight may be desirable provided that it does not trigger a laxative effect. Breaking the dosage into three or four parts taken at different times of day helps prevent laxative effect. Magnesium hydroxide is NOT recommended because of poor bioavailability and because they know of no instance of it having any beneficial use other than as a laxative. Other Magnesium compounds appear to be better, including Magnesium oxide, Magnesium sulphate, and Magnesium citrate. Natural magnesium in water (magnesium carbonate dissolved in CO2-rich water) is 30% more bio-available than Magnesium in food or pill, and offers much greater cardio-protection. If pills are used, they suggest chelated, Krebs cycle, with several Magnesium compounds; this gives greater bio-availability, and doesn't upset the stomach.

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(II) *Trigger Management*

***Second*, trigger management** is important in preventing Migraine attacks. Triggering factors can cause Migraine, and if recognized and/or avoided, may impede an impending attack. Triggers vary from person to person.

Examples of what **ARE** triggers include changes in weather or air-pressure, bright sunlight, glare, fluorescent lights, chemical fumes, menstrual cycles, and certain foods such as processed meats, red wine, beer, dried fish, broad beans, fermented cheeses, aspartame, and MSG.

Examples of what **ARE NOT** triggers include lifestyle, ***stress***, anxiety, worry, emotion, excitement, depressions, and caffeine. Unlike many articles mistakenly state, caffeine, which constricts blood vessels, is not a trigger, and, in fact, may help relieve mild Migraine pain caused by vasodilatation.

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(III) *Attack-Aborting*

***Third*, attack-aborting** medications are used to relieve the severity and/or duration of Migraine and associated symptoms. In general, most attack-aborting medication should be taken as early as possible in an attack. Many Migraineurs learn to recognize their prodrome, others can use their aura as early warning systems to implement their abortive treatment of choice for an early intervention approach, many times avoiding a severe painful prolonged attacked.

Certain **cerebral vasoconstrictor abortive agents** are designed specifically for Migraine. They may be administered by subcutaneous, oral, rectal, or intramuscular means. These medications include ergotamine tartrate, dihydroergotamine (Migranal®, DHE45®), sumatriptan (Imitrex®), naratriptan (Amerge®), rizatriptan (Maxalt®), zolmitripan (Zomig®), Electriptan (Relpax®), frovatriptan (FROVA®) and isometheptene mucate (Midrin®). Maxalt® and Zomig® both come in a melting tablet version you can take with out water, which is very convenient for early intervention for a oncoming severe attack when you may not be able to make it to a restroom. Such as air travel or perhaps a class or meeting. Even more refined 'triptans' are under development as well. Click here for more detailed information.

An excellent **non-vasoconstrictive abortive agent** is butorphanol tartrate (Stadol NS®) offered in patient administered injection and now a nasal spray. In an ER (Emergency Room) environment narcotic injections, usually taken with promenthazine (Phenergan®) or hydroxyzine (Vistril®) for nausea, can offer a non-cerebral vasoconstrictive option if all the above fail or are not appropriate (such as heart disease of other limiting medical condition). Click here for more detailed information.

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(IV) *General Pain Management*

Fourth and last, **general pain management** may include the prescription of **narcotic analgesics** which act on the central nervous system and alter the patient's perception of pain. These drugs generally relieve pain. However, because they are narcotic, they may be addictive, and such usage should be done in an appropriate manner to return a reasonable quality of life for the intractable Migraine sufferer. These medications include Fiorinal® with codeine, codeine, Percodan®, Demerol®, Tylox®, or methadone to name a few of the most well known. Click here for more detailed information and a complete list.

In addition, there are some strong **non-narcotic analgesics** that are very effective too, such as Midrin® or Fiorinal®. Click here for more information and a more detailed list.

NSAIDs (non-steroidal anti-inflammatory drugs) act by inhibiting blood vessel inflammation. NSAIDs are not specific, do not treat associated Migraine symptoms, and can cause gastrointestinal disturbances. These medications include naproxen, ibuprofen and ketorolac. You will notice that some of these over the counter NSAIDs have been repackaged to target our disease demographic such as Advil Migraine®, although these NSAIDs may look like a new Migraine OTC, but they are not, but are rather an effective OTC treatment for use with mild to mild-to-moderate Migraines for some Migraineurs. But we might suggest if do you find sufficient relief with these OTC drugs, please still advise your attending physician or Migraine specialists of the addition to these treatments to whatever you are currently prescribed. Always keep your doctor advised any self-modifications to the regime the two of you have decided to use to manage your Migraines. Click here for more information.

Simple analgesics, available over-the-counter (OTC), are generally used for mild pain. They relieve pain by acting on peripheral pain receptors. (Some analgesics also have anti-inflammatory effects). Though readily available, they are generally not strong enough to relieve Migraine pain and overuse may cause rebound headaches. These medications include acetaminophen and aspirin, and include the newly released medication Excedrin® Migraine, which is the same exact medication as Extra Strength Excedrin®, but with a new package and new name. But we might suggest if do you find sufficient relief with these OTC drugs, please still advise your attending physician or Migraine specialists of the addition to these treatments to whatever you are currently prescribed. Always keep your doctor advised any self-modifications to the regime the two of you have decided to use to manage your Migraines. MAGNUM is working to alleviate any misuse of and misperceptions about Excedrin Migraine® & other OTC analgesic products remarketed for Migraine. Click here for more detailed information.

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Prophylactic treatment of migraine

Introduction

The opportunity to choose a specific prophylactic therapy for a patient depends upon the severity of the attacks and how these headaches alter the quality of life. Prophylactic treatment is usually recommended in the case of 3 or more severe attacks per month incompletely responding to symptomatic treatment and in the case of more than 4 days with headache per month.

The main goals for preventive agents in migraine treatment are to reduce the frequency and severity of migraine attacks and improve the quality of life. It is generally accepted that a good response to prophylactic treatment is at least a 50% reduction in the frequency or severity of migraine attacks. Others goals are to expand the knowledge of preventive treatments, to promote studies in this field, and to avoid the development of a chronic daily headache as well as symptomatic drug abuse or misuse [1].

As for all therapeutic strategies, even the prophylactic drugs for migraine should undergo a careful evaluation of their benefit/risk ratio. This implies that each treatment should be used at the dosage with the least number of adverse drug reactions (ADRs) in order to reduce the number and severity of attacks for an adequate period until the treatment can be stopped.

The presence of any comorbid conditions should be considered in the choice of a preventive medication for migraine.

From evidence-based medicine to recommendations

Recommendations for the prophylactic treatment of migraine should be not just the simple sum of the findings of clinical trials from evidence-based papers, obtained from Medline, but also the result of the critical evaluation by a group of experts who discuss the results available in the literature, taking into account their own experiences. In fact, clinical reports may not be sufficient for giving a step approach to treatment choice, particularly for drugs not yet adequately evaluated, even if they are used by patients or prescribed by physicians [2–4].

Management of pharmacological treatment

To minimize the risk and improve the patient's compliance, prophylactic treatment should be started at low doses, possibly as a monotherapy. Doses can be slowly increased until therapeutic goals are achieved in the absence of side effects. The treatment should be maintained for at least 3 months before stopping it. In fact, clinical benefit may take as long as 1–3 months after the onset of response. To use a monotherapy at adequate doses and for an adequate period of time is necessary in order to underscore the relationship between drug efficacy and side effects.

Long-acting or depot formulations can improve patient compliance. When pharmacological resistance appears, a new prophylactic treatment with another drug should be preceded by a washout period.

Drugs contraindicated for any comorbid conditions (i.e. beta-blockers in patients with asthma) and drugs that could worsen migraine (i.e. nifedipine for hypertension) should be avoided, when possible.

Particular attention should be devoted to drug-drug or drug-food interactions, and it should be remembered that many prophylactic treatments may cause teratogenic effects. Therefore, prophylactic treatment during pregnancy should be limited to special situations, and in these rare cases, drugs with the lowest risk to the fetus should be selected.

Patient recommendations

The main problem in preventive therapies is always patient compliance. The compliance in prolonged treatments is inversely related to the length of treatment and the number of pills taken every day. Therefore, when possible, the number of drugs taken should be reduced and the patients should be involved in the choice of their own treatment. Patients should be carefully informed about how and when to take drugs, and about the potential adverse effects. Another relevant point to address is the patient's expectations of the actual therapeutic efficacy of the drug, and about the impact of the treatment on the quality of life and disease evolution.

For the evaluation of the efficacy of the treatment, patients should be educated to follow a formal management plan and to carefully fill out headache diaries that record the frequency and duration of attacks, the severity of pain, the functional impairment, disability and the drugs taken as well as any adverse events. These parameters are necessary to assess the modifications in migraine due to preventive treatment.

Primary prevention of migraine

Migraine can be considered as a particular response of the human brain to a number of triggers, both internal and external. Such response is probably genetically determined. Migraine patients seem to present a lower threshold for attacks in certain brain areas compared with those of non-migraineurs. In this regard, the primary prophylaxis of migraine should be focused on identifying the triggers and carefully avoiding them by changing the patient's lifestyle. Therefore, patients should be provided a list of common triggers to avoid. Another easy method is encouraging patients to note all the migraine attacks and the potential triggers for each attack in their headache diary.

The most frequent trigger factors are listed in Table 1. However, even a correct lifestyle cannot prevent all migraine attacks in all patients.

It has been hypothesized that migraine patients have a lowered threshold for trigger factors, perhaps genetically determined. So, a rational prophylactic treatment should be focused to enhance this threshold and this, together with the removal of trigger factors, when possible, should result in the reduction of the number and intensity of attacks.

Precipitating factors are those factors able to elicit a migraine attack, after a short time of exposure. They are not the cause of migraines. They often need cofactors to precipitate the attacks and, even in the same patients, one factor is not enough to always induce the attack.

One or more precipitating factors are reported in 64%–90% of patients with migraine, and these are more frequent in those with migraine without aura than with aura. The most frequent factors are stress and psychological tension.

A trivial trigger is considered food. Many people believe that by avoiding some specific foods it is possible to reduce the frequency of migraine attacks. Putative allergic factors are often considered responsible for migraine attacks, whereas, only in rare cases, a specific food directly causes migraine. From 20% to 52% of patients report that alcoholic drinks precipitate migraine, and conflicting data have been reported with respect to differences between beer or red and white wine. Also, some foods are involved as precipitating factors in percentages varying from 10% to 45%, namely: chocolate, cheese, some fruits, citrus fruits, fatty foods and fried foods. Peatfield [5] recorded 19% of patients reporting sensitivity to cheese, chocolate, or both, and 11% of patients sensitive to citrus fruits. The exact mechanism of these migraine attacks is unknown, although migraine is generally believed to be caused by a chemical reaction consisting in the release of serotonin from the intestinal wall, or by an enzymatic defect, and not by allergic reactions.

By contrast, fasting has been described to be a precipitating factor in 25% of children and in 40% of adults affected by migraine.

Menstruation is a common precipitating factor in 24%–64% of women suffering from migraine without aura. In fact, hormonal factors can be considered as both precipitating and predisposing factors.

Both too much or too little sleep as well as fatigue are believed to be precipitating factors.

Moreover, weather changes are often considered to be precipitating factors for migraine in a percentage ranging from 7% to 43%, and patients even say that they are able to predict the forecast. By contrast, specific studies did not show a relationship between migraine attacks and either weather conditions or barometric changes.

Glaring, blinding and psychedelic lights are also reported to be precipitating factors for migraine, and in a recent study these lights were recognized as precipitating factors only in migraine with aura [6].

Other triggers could be angiographic procedures, head injuries, physical exercise, and altitude. By contrast, sexual activity does not seem able to cause a migraine attack.

Behavior modifications

The first recommendation for patients should be to avoid trigger factors. To obtain this result, patients need to recog-

nize their specific trigger factors; therefore, it is necessary to carefully fill out the diary that should be evaluated at every medical visit.

When stress is identified as the main trigger factor, it is useful to begin a formal behavioral treatment program to avoid stressors, since pharmacological therapy alone is unable to control migraine attacks. For this purpose, muscle relaxation techniques, including biofeedback, are recommended. In some cases physical exercise can be useful to reduce stress.

Drug treatment should be used together with behavior modifications to obtain a significant reduction of migraine attacks and an improvement in the quality of life.

Re-evaluation of the diagnosis

The diagnosis should be re-evaluated when:
- there is a case of high frequency of migraine attacks
- there are changes in migraine characteristics (i.e. focal symptoms, variation of frequency, intensity or length of attacks, etc.)
- there is a lack of effects after three treatments with different drugs
- there is an analgesic abuse

Drugs for prophylactic treatment

A few drugs for the prophylactic treatment of migraine have been studied in adequate clinical trials according to evidence-based medicine (EBM) criteria. The level and quality of evidence for their use, and the overall recommendation level, are presented in Tables 2 and 3 respectively. Clinically relevant drug-drug interactions are given in Table 4.

Beta-blockers

How beta-blockers can reduce attack frequency in migraneurs is not clear, although it is probably by acting on the central monoaminergic system and serotonin receptors. Not all these drugs are effective, and those used in migraine prophylaxis include atenolol, metoprolol, nadolol and propranolol [7–56]. Beta-blockers are contraindicated in patients with chronic obstructive pulmonary disease, diabetes mellitus, heart failure and peripheral vascular diseases. There is a relative contraindication in pregnancy.

Atenolol and nadolol are excreted by the kidneys and show fewer adverse effects in the central nervous system (CNS). Failure of prophylactic treatment with one beta-blocker is not predictive of the activity of other beta-blockers, so that consecutive trials with these drugs are appropriate. Physicians should start with low doses and increase them slowly, if necessary.

When migraine attacks are controlled, doses can be reduced slowly. The abrupt suspension of beta-blockers can induce rebound effects both increasing migraine attacks and inducing adrenergic side effects and hypertension.

Calcium channel blockers

Calcium channel blockers act by modulating neurotransmission, inducing vasodilatation and exerting a cytoprotective effect by preventing the influx of calcium ions into the cells and reducing cell damage due to hypoxia. The therapeutic effects become evident only after some months of treatment, and are associated with a number of side effects. Among all available drugs of this class, the most used are flunarizine (level of evidence A, recommendation level I) and verapamil (level of evidence B, recommendation level II) [57–77]. The efficacy of these drugs in reducing migraine attacks by at least 50% and improving the quality of life is comparable with that obtained by beta-blockers at least for flunarizine. Less consistent are the findings with nimodipine and nifedipine [78–82].

Some calcium channel blockers are contraindicated in pregnancy, hypotension, heart failure, atrioventricular (AV) block, Parkinson's disease and depression (e.g. flunarizine) and in patients in therapy with beta-blockers and monoamine oxidase inhibitors (MAOI) (e.g. verapamil).

Serotonin antagonists

Pizotifen is one of the serotonin receptor antagonists with weak antihistaminic and cholinergic effects. Despite its effectiveness in migraine, with a clinical benefit in 50%–64% of the cases, it has side effects which include weight gain and asthenia (level of evidence A, recommendation level IIIb) [83–86]. Methysergide is a semisynthetic ergometrine derivative with activity as 5-HT_1 and 5-HT_2 receptor antagonists. It has been shown to be active, particularly in cases with high frequency of attacks not responsive to treatment [86]. Contraindications include pregnancy, peripheral vascular disorders, severe arteriosclerosis, coronary artery disease, severe hypertension, thrombophlebitis or cellulitis of the legs, peptic ulcer disease, fibrotic disorders, lung diseases, connective

tissue disease, liver or renal function impairment, valvular heart disease, cachexia, or serious infection. Methysergide can induce retroperitoneal fibrosis and pleural and heart valve fibrosis with an estimated incidence of 1 in 5000 treated patients. Therefore, it should be reserved for severe cases in which other migraine preventive drugs are not effective, taking carefully into account the risk-benefit ratio. Today this drug is not available in Italy.

Tricyclic antidepressants

Amitriptyline is useful in migraine, especially in patients with concomitant tension-type headache (level of evidence A, recommendation class I). The mechanism of action is not related to its antidepressant activity. Amitriptyline modulates monoaminergic pathways, by inhibiting the reuptake of both adrenaline and serotonin. Moreover, it functionally down-regulates β-adrenergic and serotonergic receptor expression in the central nervous system. The effective dose varies [27, 87–91], starting with an initial dose of 10 mg, per os, every night, to be increased by 10 mg per week, up to a maximum of 50 mg per day. High doses could be necessary in the case of concomitant depression.

A lower risk of developing asthenia and anticholinergic side effects has been observed for nortriptyline compared to amitriptyline (level of evidence C). The contraindications include: severe cardiac, liver, renal, prostatic and thyroid diseases, glaucoma, hypotension, convulsive disorders and concomitant use of MAOI.

Tricyclic antidepressants should be used with caution in elderly patients because of anticholinergic effects.

Selective serotonin-reuptake inhibitors

Few studies are available on the use of this class of drugs in the prophylaxis of migraine [92–98]. At the moment, there is no definitive evidence supporting the use of these drugs in preventing migraine attacks.

Alpha-2 agonists

The majority of the studies on the prophylactic treatment of migraine concern clonidine but failed to show more efficacy compared with placebo [99–113]. Negative results were also obtained with guanfacine [114].

Antiepileptic drugs

Sodium valproate shows excellent results in preventing migraine in clinical trials (level of evidence A; recommendation level I) [115–120].

Care should be used when this drug is associated with acetylsalicylic acid (ASA) and warfarin, because of the possibility of bleeding. The main side effects are nausea, alopecia, tremors and weight gain; chronic use may induce liver damage, mostly in children. This drug is teratogenic and should not be administered to pregnant women.

Gabapentin, a GABAergic drug, has been shown to be effective in preventing migraine attacks [121, 122]. In a recent multicenter double-blind placebo-controlled study, this drug was significantly more effective than placebo in reducing the frequency of migraine attacks [122]. The more frequent adverse effects were somnolence and dizziness.

Topiramate and lamotrigine have been used with moderate efficacy in migraine prophylaxis [123–130]. The most frequent side effects of topiramate were cognitive dysfunction, sedation, diarrhea, weight loss, and dizziness. Recently, it has been reported that after one month of therapy with topiramate, some patients reported an acute reduction of vision, myopia and acute narrow-angle glaucoma.

Lamotrigine showed less efficacy in preventing migraine without aura, whereas it was efficacious in preventing attacks in the case of a high frequency of migraine with aura crises [128–130]. The most frequent side effects were: rash (some fatal), fatigue, dizziness, headache, Stevens-Johnson syndrome, toxic epidermal necrolysis and hypersensitivity reactions.

No recent studies have been carried out on carbamazepine as a prophylactic antimigraine drug and data are inconclusive about its efficacy [131, 132].

Non-steroidal anti-inflammatory drugs

The main mechanism of action of non-steroidal anti-inflammatory drugs (NSAIDs) is the inhibition of cyclooxygenase in both isoforms, whereas, even in the absence of inflammation, NSAIDs are active in reducing migraine pain (level of evidence B, recommendation level II). Among this class of drugs, acetylsalicylic acid, flurbiprofen, lornoxicam, mefenamic acid, ketoprofen and both naproxen and naproxen sodium show a discrete effectiveness in migraine prophylaxis [2, 133–146]. Both naproxen and naproxen sodium are useful in the prevention of menstrual migraine (level of evidence B; recommendation level II) [147, 148].

NSAIDs should be used for intermittent prophylaxis in menstrual migraine and not for prolonged periods of time because of their gastric and intestinal side effects (level of evidence B) [149, 150].

Dihydroergotamine

Dihydroergotamine in slow-release formulations at various doses was effective in preventing migraine attacks [151, 152]. Dihydroergokryptine also appeared to be an effective drug for the prophylaxis of migraine attacks [153].

Lisuride

Lisuride has been proved to be effective and well-tolerated for migraine prophylaxis in some studies [154, 155]. In an open study, a reduction of more than 50% of attacks was observed in 61.4% of patients treated for a 3-month period, with good tolerance [154].

Riboflavin

Riboflavin at high doses (up to 400 mg) showed good effectiveness in preventing migraine attacks [156] with a low rate of unwanted side effects, such as mild abdominal pain and diarrhea. This drug at these doses is not available in Italy.

Estrogens

Some clinical trials showed the efficacy of high doses of estradiol (1.5 mg/day in gel) in the prophylactic treatment of menstrual migraine. They have been demonstrated to significantly reduce the number of attacks [157, 158]. Lower doses (50 mg/day) were ineffective. Preliminary studies suggest a possible effectiveness of the association of estradiol with flumedroxone and methysergide [86].

Tanacetum parthenium

The efficacy of feverfew in preventing migraine is not universally accepted. Some studies show a reduction in pain intensity and associated symptoms, whereas others show an increase in the frequency of attacks or no differences in comparison with placebo [159–162].

Magnesium

Magnesium showed efficacy in preventing migraine in three clinical trials [163–165].

Table 1 Common trigger factors for migraine

Hormonal	Menstruation, ovulation, oral contraceptives
Diet	Alcohol, nitrites, monosodium glutamate, aspartame, chocolate, cheeses, fasting
Psychological	Stress, post-stress (weekends and holidays), anxiety, fear, depression
Environmental	Flashing lights, blinding lights, fluorescent lights, weather changes, perfumes, altitude
Sleep	Lack of or excessive sleep
Drugs	Nitroglycerin, histamine, reserpine, hydralazine, ranitidine, estrogens, cocaine, marijuana
Others	Head injuries, physical exercise

Table 2 Evidence for prophylactic drug treatments in migraine. Dose ranges are indicative only. Recommendations are not made for regimen dosing. Refer to published literature for specific dosing information. No dosing information is provided for treatments not evidence-based (Level C)

Drug	Level of evidence	Scientific strength of evidence	Clinical effectiveness	Adverse events	Comments
Beta-blockers					
Atenolol DT, 100 mg/day ED, 100 mg/day	A	++	+++	Occasional, not severe	Frequent AEs are asthenia, fatigue and dizziness. Useful in patients with hypertension, anxiety and panic attacks. Should not be used in patients with coexisting asthma, cardiac failure or Raynaud's disease. May exacerbate depression. Do not use with ergotamine. Increase doses gradually
Propranolol DT, 40–240 mg/day ED, 80–240 mg/day	A	+++	+++	Occasional, not severe	Same as for atenolol, plus essential tremor. When propranolol is used with rizatriptan, a lower dose of rizatriptan should be administered
Nadolol DT, 80–240 mg/day ED, 80–240 mg/day	B	+	++	Occasional, not severe	Same as for atenolol
Metoprolol DT, 50–300 mg/day ED, 200 mg/day	B	++	++	Occasional, not severe	Same as for atenolol
Calcium channel blockers					
Flunarizine DT, 3–10 mg/day ED, 3–10 mg/day	A	+++	+++	Occasional, not severe	Most frequent side effects are weight gain and sedation. Depression and extrapyramidal symptoms may be observed in elderly patients. The recommended dose to reduce AEs is 5 mg/day
Cinnarizine DT, 75–150 mg/day ED, 75–150 mg/day	B	+	+	Occasional, not severe	Drowsiness and weight gain
Nimodipine DT, 60–120 mg/day ED, 120 mg/day	B	+	+	Occasional, not severe	Abdominal discomfort is usual. Elevated cost
Verapamil ED, 240 mg/day	B	+	+	Occasional, not severe	Constipation is common. Do not use in the presence of AV block. Could be a good alternative for beta-blockers in athletes. Recommended in patients with stroke or prolonged aura, and in patients with coexisting hypertension and tachycardia. Avoid association with beta-blockers
Diltiazem[a]	C	NA	?	Occasional, not severe	Tolerability similar to other drugs of this class. Recommended dose to minimize side effects is 5 mg/day

the table continues →

Continuation of Table 2

Drug	Level of evidence	Scientific strength of evidence	Clinical effectiveness	Adverse events	Comments
Antidepressants					
Tricyclic antidepressants (TCAs)					
Amitriptyline DT, 25–150 mg/day ED, 30–150 mg/day	A	+++	+++	Frequent, not severe	Drowsiness, weight gain and anticholinergic AEs are common. Particularly useful in patients with depression, migraine and tension-type headache. A progressive increase in doses is recommended until maintenance doses are reached in order to reduce AEs (recommended doses, 10–75 mg/day)
Nortriptyline	C	NA	+	Frequent, not severe	Better tolerated than amitriptyline (doses, 10–75 mg/day)
Doxepin, imipramine[a]	C	NA	+	Frequent, not severe	See other TCAs
Selective serotonin-reuptake inhibitors					
Fluoxetine DT, 10–40 mg/day	B	++	+	Occasional, not severe	Insomnia, fatigue, tremor and stomach pain are frequent. Used as an adjunct treatment in depressed patients. There are drug interactions with 5-HT agonists
Fluvoxamine, paroxetine, sertraline[a]	C	NA	+	Occasional, not severe	Same as for fluoxetine
Monoamine oxidase inhibitors[a]	C	NA	?	Frequent and potentially severe	Requires complex management with special dietary restrictions; shows a high risk of severe drug-drug interactions. Benefits are less than potential risks
Other antidepressants					
Bupropion, mertazepine, trazodone, venlafaxine[a]	C	NA	+	Occasional, not severe	Could be useful in patients with depression and anxiety disorders
Antiepileptics					
Sodium valproate DT, 800–1550 mg/day Serum level, 50 mg/l ED, 900–1500 mg/day	A	+++	++	Frequent, not severe	Recommended for patients with prolonged or atypical migraine aura. Not recommended in patients with liver disease and hemorrhagic diatheses. A progressive increase in doses is recommended with repeated monitoring of drug plasma levels in the early months of treatment. AE like nausea, asthenia and somnolence are frequently seen when higher doses are used. Other side effects include weight gain, hair loss, tremor, and teratogenic potential
Gabapentin DT, 900–1200 mg/day	A	++	++	Occasional, not severe	
Topiramate[a]	B	++	?	Occasional, not severe	Occasional CNS AE, kidney stones and weight loss (100 mg/day). Acute myopia and narrow-angle glaucoma

the table continues →

Continuation of Table 2

Drug	Level of evidence	Scientific strength of evidence	Clinical effectiveness	Adverse events	Comments
Lamotrigine DT, 100 mg/day	B	++	?	Frequent, not severe	Recommended for migraine with aura with a high frequency of attacks
Carbamazepine[a] DT, 600 mg/day	B	++	0	Frequent, not severe	Common adverse events are dizziness, vertigo, drowsiness. Not recommended because of poor efficacy and a high incidence of side effects
Alpha-2 agonists					
Clonidine DT, 0.05–0.225 mg/day ED, 0.075–0.15 mg/day	B	0	0	Frequent, not severe	CNS adverse events frequent, no clinical benefit for prevention of migraine
Serotonin antagonists					
Pizotifen DT, 150 mg/day ED, 150 mg/day	A	++	+++	Frequent, not severe	Somnolence and weight gain are common
Cyproheptadine[a]	C	NA	+	Frequent, not severe	Used in pediatric migraine. Weight gain and fatigue are common AE
Lisuride[a]	A	++	+	Occasional, not severe	Not available in Italy. At low doses useful for migraine prophylaxis
Dihydroergotamine TR DT, 10 mg/day ED, 10 mg/day	A	++	+++	Rare, not severe	Alternative drug for moderate to severe migraine attacks of low frequency and in case of no response to triptans. Do not use within 6 h after triptans. To be used in mild to moderate migraine attacks when NSAIDs are not tolerated. Useful for short-term prophylactic therapy
NSAIDs					
Acetylsalicylic acid DT, 325–1300 mg/day ED, 1300 mg/day	B	+	?	Occasional, not severe	Abdominal discomfort, gastritis and occult GI bleeding are frequent. May be useful for patients with arthritis and previous stroke
Lornoxicam[a]	B	++	?	Occasional, not severe	–
Naproxen, naproxen sodium DT, 1100 mg/day ED, 1100 mg/day	B	++	?	Occasional, not severe	Used as short-term prophylaxis in menstrual migraine
Ketoprofen DT, 150 mg/day ED, 150 mg/day	B	++	?	Occasional, not severe	–

the table continues →

Continuation of Table 2

Drug	Level of evidence	Scientific strength of evidence	Clinical effectiveness	Adverse events	Comments
Others					
Estradiol DT, 15 mg/day for 1 week ED, 15 mg/day for 1 week	B	++	++	Rare, not severe	Used for the short-term prevention of menstrual migraine. Percutaneous use
Vitamin B2 DT, 400 mg/day ED, 400 mg/day	B	+++	++	Rare, not severe	Rare AE. Unknown drug-drug interactions
Magnesium DT, 400–600 mg/day ED, 400–600 mg/day	B	+	+	Rare, not severe	Non-chelated formulations can induce diarrhea. May be useful in patients with menstrual migraine
Tanacetum parthenium DT, 50–82 mg/day ED, 50–82 mg/day	B	++	?	Rare, not severe	Mild side effects. Withdrawal could be associated with rebound frequency of headaches
Botulinum toxin A	B	++	++	Rare, not severe	Techniques of administration are not easy and applicable everywhere
Drugs not available or not used in Italy					
Vigabatrin[a] DT, 1000–2000 mg/day	B	++	?	Occasional	Clinical experience and published data are lacking and further studies are needed. Visual field constriction has been described as AE
Phenelzine[a]	C	NA	?	Frequent	Requires complex management with special dietary restrictions. High potential for drug-drug interactions. May be helpful in patients with coexisting depression or when antidepressants from other classes fail. AE include orthostatic hypotension, fatigue, vertigo and psychotic disturbances
Timolol DT, 20–30 mg/day ED, 20–30 mg/day	A	++	?	Infrequent	–
Dihydroergokryptine[a] DT, 20 mg/day	B	+	?	Not severe	Mild side effects. Withdrawal could be associated with rebound frequency of headaches
Methylergonovine[a]	C	NA	?	Frequent	May be used in menstrual-associated migraine
Methysergide[b] DT, 2–10 mg/day ED, 6 mg	A	+++	?	Rare but potentially severe	Should be reserved for severe cases in which other migraine preventive drugs are not effective
Flumedroxone DT, 10–30 mg/day ED, 10–30 mg/day	B	+	?	Occasional to frequent	Rare AE are hepatic disease, hemorrhage, cholestatic jaundice, porphyria, menstrual disturbances in women, and drowsiness and decreased libido in men

[a] Efficacious dose not established in controlled trials; [b] Based on body weight

CNS, central nervous system; *AE*, adverse events; *TCAs*, tricyclic antidepressants; *AV*, atrioventricular; *NSAIDs*, non-steroidal anti-inflammatory drugs; *GI*, gastrointestinal; *DT*, doses tested; *ED*, efficacious doses in clinical trials; *TR*, time-released; *NR*, not recommended; *NA*, not applicable; ?, undetermined

Table 3 Drugs for prophylactic treatment of migraine grouped by level of recommendation

Level I	Level II	Level III [a, b]	Level IV
Amitriptyline	Cinnarizine	Acetylsalicylic acid[b]	Bupropion
Atenolol	Dihydroergotamine TR	Botulinum toxin A[a]	Carbamazepine
Flunarizine	Fluoxetine	Diltiazem[a]	Clonidine
Propranolol	Gabapentin	Fluvoxamine[a]	Dihydroergokryptine*
Sodium valproate	Lamotrigine	Lisuride[a]	Doxepin
	Lornoxicam	Magnesium[a]	Estradiol
	Metoprolol	Methylergonovine[b]*	Flumedroxone*
	Nadolol	Nimodipine[a]	Imipramine
	Naproxen	Nortriptyline[a]	Ketoprofen
	Naproxen sodium	Paroxetine[a]	Mertazepine
	Topiramate	Pizotifen[b]	Methysergide*
	Verapamil	Sertraline[a]	Phenelzine*
	Vitamin B2		Tanacetum parthenium
			Timolol*
			Trazodone
			Venlafaxine
			Vigabatrin*

The names of the drugs are listed in alphabetical order

* Drugs unavailable or not used in Italy

[a] and [b] refer to the two subgroups of Level 3 reported in Table 7 "Levels of recommendation for the treatment of migraine and cluster headache" of the Methodology section

[a] Drugs with no severe adverse events

[b] Unsafe drugs or with complex indication for use (e.g. special diets) or important pharmacological interactions

Table 4 Clinically relevant drug-drug interactions among antimigraine drugs

Drug 1	Drug 2	Effect	Onset	Probable mechanism of action
Acetylsalicylic acid (ASA)	Diclofenac	GI lesions	Rapid	Gastric irritation
	Indomethacin	GI lesions	Delayed	Gastric irritation
	COX-2 inhibitors	Increased risk of GI bleeding	Delayed	Gastric irritation
Ergotamine	Triptans	Vasoconstriction	Rapid	Additive vasoconstrictive effects
Methysergide	Triptans	Prolonged vasoconstriction	Rapid	Additive vasoconstrictive effects
NSAIDs	NSAIDs	Peptic ulcer; gastritis; GI bleeding	Rapid	Gastric irritation
Propranolol	Rizatriptan	Increased rizatriptan levels	Rapid	Inhibition of rizatriptan metabolism
SSRIs	Triptans	Serotonin syndrome	Rapid	Excessive 5-HT stimulation
	MAOI	Serotonin syndrome	Rapid	Excessive 5-HT stimulation
TCAs	Sertraline	Serotonin syndrome	Rapid	Excessive 5-HT stimulation
Triptans	Triptans	Prolonged vasoconstriction	Rapid	Additive vasoconstrictive effects
	MAOI	Serotonin syndrome	Rapid	Excessive 5-HT stimulation
Valproate	Amitriptyline	Increased amitriptyline levels	Delayed	Inhibition of amitriptyline metabolism
Verapamil	Beta-blockers	Hypotension, bradycardia	Rapid	Additive cardiovascular effects, reduced metabolism of beta-blockers

GI, gastrointestinal; *NSAIDs*, non-steroidal anti-inflammatory drugs; *SSRIs*, selective serotonin-reuptake inhibitors; *TCAs*, tricyclic antidepressants; *MAOI*, monoamine oxidase inhibitors

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